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Abstract

In December 2001, a fatal case of pneumococcal meningitis in a Marine Corps recruit was identified. The pneumococcal isolate was serotype 38, a serotype not covered by current pneumococcal vaccine formulations. This is the first report in North America of invasive disease due to this potentially emerging pathogen.

Introduction

In December 2001, the Department of Defense Center for Deployment Health Research at the Naval Health Research Center (NHRC) was consulted regarding a case of fatal meningitis caused by *Streptococcus pneumoniae* (pneumococcus) in a Marine Corps recruit.

The pneumococcus is a common cause of fatal bacterial meningitis in the United States [1]. A 23-valent polysaccharide and 7-valent conjugate pneumococcal vaccine are available and effective in protecting against serotype-specific invasive infections. For this reason, it is important to determine whether clinically significant pneumococcal infections are vaccine-covered serotypes, particularly in settings like military training camps where epidemic spread can occur.

Clinical Course

On the morning of December 22, 2001, an 18-year-old Caucasian male in his eighth week of Marine Corps basic training failed to complete his physical training course and presented to the field medical station in emotional distress with a headache and an episode of vomiting after physical training.

His neurological symptoms progressed over the next 10 hours until he became disoriented and unresponsive. He was admitted to the local hospital emergency department where fever and coma were observed. Despite rapid initiation of intravenous ceftriaxone, ampicillin, and vancomycin in the emergency room, the patient's condition remained unimproved. He was transferred to the ICU of a tertiary care hospital on ventilator support. Intravenous

dexamethasone was initiated; antibiotics and supportive care were continued. He died approximately 30 hours after his initial presentation to the field medical station.

The patient had no previous history of neurological or other medical problems and was not taking any medications. He received meningococcal vaccination (Menomune A/C/Y/W135, Aventis Pasteur) on October 31, 2001. He had no history of receiving pneumococcal vaccination.

Laboratory Evaluation

Lumbar puncture performed during medical work-up of the patient revealed an opening pressure greater than 500 mm; cerebrospinal fluid (CSF) was milky white, with a glucose concentration of 3 mg/dl and total protein of 269 mg/dl. White count in the CSF was 4444 with 91% segmented neutrophils, and microscopic evaluation of the CSF revealed Gram-positive diplococci. Blood and CSF cultures were positive for *Streptococcus pneumoniae*, sensitive to all antibiotics tested. Streptococcal culture of the throat was negative.

A pneumococcal isolate from the blood was sent to the Respiratory Disease Laboratory at NHRC for additional evaluation. Serotyping was performed using a modified version of the latex agglutination typing method [2]. Samples were tested against antisera for vaccine-covered serotypes (Statens Serum Institut, Denmark) and results confirmed using the classic Quellung reaction and multi-locus sequence typing (MLST) technique.

For MLST, chromosomal DNA was extracted using spin DNA extraction columns (Qiagen, Valencia, CA). A subsequent PCR reaction was carried out in 100- μ l volumes, using primer pairs

developed by Enright and Spratt [3]. Each of the primer pairs amplify an internal fragment of 7 housekeeping genes: *aroE*, *gdh*, *gki*, *recP*, *spi*, *xpt*, and *ddl*. Amplified DNA fragments were purified using QIAquick purification columns (Qiagen, Valencia, CA) and directly sequenced in each direction on an automated sequencer with Big Dye terminator chemistry (Applied Biosystems, Foster City, CA). Allelic matches at each loci were determined through a search engine at the pneumococcal MLST Web site (<http://www.mlst.net>).

Using the classic serotyping methods outlined, the isolate did not react with any of the 23-valent vaccine-specific typing antisera. Molecular investigation utilizing MLST demonstrated an allelic profile that matched sequence type 393. Using the MLST database, this sequence type matched a definitive pneumococcal serotype 38 (PS38). The latex agglutination was repeated using antisera against this serotype, and results were confirmatory.

Discussion

PS38 is not covered in the current 23-valent polysaccharide or the 7-valent conjugate pneumococcal vaccine formulations, which cover serotypes that are the most common causes of invasive and antibiotic-resistant infections in the United States. Given the rapidly fatal outcome in this case and the importance of vaccine formulations being appropriately targeted, the medical literature was reviewed to determine PS38 prevalence in the United States and globally.

Within the United States, only 1 other case of PS38 disease was found. This case was an elementary school student with conjunctivitis [4].

Globally, a review of the medical literature demonstrated several reports of disease caused by PS38. All were associated with meningitis. In the late 1970s, researchers in Egypt collected 131 CSF pneumococcal isolates from meningitis patients admitted to hospitals in the Cairo area [5]. PS38 was found in 3 (2.29%) of the isolates and ranked as the 13th most common serotype out of the 34 isolates identified. Cases were reported in children under age 12 and in 1 adult greater than 36 years old. In South Africa, other researchers identified 2 cases of meningitis caused by PS38 [6]. This serotype was ranked the 28th most common serogroup out of 33 serogroups identified from 1016 specimens collected from 1979 to 1986. Antibiotic-resistance testing was performed in this study and found PS38 to be pan-sensitive to the antibiotics tested.

In South America, researchers processed 1000 isolates from CSF specimens collected in São Paulo, Brasil from 1977 to 1988 [7]. Thirteen specimens (1.3%) proved to be PS38, making it the 22nd most common serotype out of the 60 serotypes identified, affecting children, adults, and the elderly.

Cases of PS38 infection have also been reported in Eurasia. A study in southern India found 1 case of PS38 infection in a child with meningitis [8]. Out of the 18 isolates processed in 1992-1993, this serotype tied as the 5th most common isolate out of the 9 isolates recognized. Another study of meningitis cases in the Netherlands in 1994 found 3 cases of penicillin-susceptible PS38 infection out of the 153 isolates processed [9]. Out of the 31 serotypes distinguished, PS38 tied at the 14th most common serotype identified.

Meningitis caused by PS38 has not been previously reported in North America. However, researchers in Ontario, Canada, isolated PS38 from nasopharyngeal swabs in a study of pneumococcal carriage in children attending daycare from 1995 to 1996 [10]. PS38 ranked the 14th most common serotype, with 8 out of 589 (1.36%) isolates positive.

Although PS38 seems to be a sporadic cause of pneumococcal disease worldwide, it should be cause for concern. Of the PS38 disease reported internationally, all were cases of meningitis, a serious and often fatal disease. Additionally, even though all PS38 isolates tested were pan-sensitive to broad-spectrum antibiotics, antibiotics can be ineffective in a rapidly fulminating infection. This suggests considering primary measures such as vaccination for PS38 disease prevention. In some countries, PS38 was implicated in enough cases of invasive disease to be considered for inclusion into a 14- or 23-valent vaccine formulated for that region.

With the current routine use of the 7-valent conjugate vaccine, the serotype distribution in pneumococcal carriage is certain to change, selecting for carriage of nonvaccine-covered serotypes [11]. The Canadian study of PS38 carriage is of particular interest, since carriage is important in the development of disease and in transmission of the pneumococcus to others [12]. Considering the nonvaccine-covered PS38 is circulating in the United States and Canada, it is possible that PS38 carriage rates could increase, thereby increasing rates of PS38 disease and meningitis.

Conclusion

Streptococcus pneumoniae serotype 38 is an uncommon cause of pneumococcal disease in the United States and thus, is not included in commercial vaccine formulations. This is the first report of a fatal case of serotype 38 pneumococcal meningitis in North America. This review suggests that the pathogen has the potential for increased morbidity and mortality in our population. Continued laboratory-based surveillance with a focus on emerging strains is critical for development of future prevention efforts.

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